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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,625	01/14/2004	Michael Bogenstaetter	ORT1614 CON	4860

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 03/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/757,625	BOGENSTAETTER ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1/14/04* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. This action is in response to an application filed on 1/14/04. There are forty-five claims pending and forty-five under consideration. Claims 1-30 are compound claims. Claim 31 is a composition claim. Claims 32-39 are use claims. Claims 40-45 are synthesis claims. This is the first action on the merits. The application concerns some 2-oxy, 2-amino, and 2-thio-imidazole compounds, compositions, and uses thereof.

Title

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: replacing the word "Heterocyclic" with "2-Oxy, 2-Amino, and 2-Thio-imidazole".

Abstract

3. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The abstract

is too short and generic. Examiner suggests claim 1, including the figure, and the utility.

Information Disclosure Statement

4. Part of the information disclosure statement filed 1/14/04 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered. The copy of the 892 from the parent case fails to comply with requirement (4).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 and 28-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. In claims 1, 2, 28, and 40 Applicants' offer 'amido" as a possible radical Q^1, M, or Q^3. What is the structure of this radical? The Examiner understands that it is formed by removal of a hydrogen atom from the class of compounds called amides, which are the reaction products of acids and amines. However, what is the structure of the amides used to form this radical and how is it attached to the core? It is likely not attached through the carbonyl group because such compounds would fall into the next two radicals listed, $R^{M1}HNC(O)$ etc. If the amide radical is attached through nitrogen, then what acid residue is attached to nitrogen? Is it a carbon acid or are the acids of sulfur and phosphorus intended as well? If the amido group is attached through a side chain, are there any constraints on what this side chain may be? The Examiner suggests deleting this word.

6. Claims 1-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Throughout these claims, Applicants have the limitations "or a pharmaceutically acceptable ester, ether, *** amide". What are the structures of these ester, ether, or amide derivatives? In lines 8-17, page 18 there is a generic discussion of the concept of prodrug but no definition of

what ester, ether, or amides are contemplated. The Examiner suggests deleting these terms.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-39 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to convey reasonably to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. To quote the MPEP 2163 II A 2. (a) "Original claims Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention". Where are the chemical formulas found or the processes used to prepare the various claimed "pharmaceutically acceptable ester, ether, *** amide"?

8. Claims 1-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making N-oxides and salts of the claimed compounds, does not reasonably provide enablement for making hydrates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed hydrate, the lack of predictability in the art, and the broad scope of the claims.

c) There is no working example of any hydrate formed. The claims are drawn to hydrates, yet the numerous examples presented all failed to produce a hydrate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification

purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that hydrates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

g) The state of the art is that is not predictable whether hydrates will form or what their composition will be. In the language of the physical chemist, a hydrate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The water molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed hydrate, i.e. if one, two, or a half a molecule of water added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is

possible to make meta-stable non-equilibrium hydrates, further clouding what Applicants mean by the word hydrates. Compared with polymorphs, there is an additional degree of freedom to hydrate, which means a different temperature or even the moisture of the air that might change the stabile region of the hydrate.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula (I). Thus, the scope is broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

9. Claims 1-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparing compounds labeled with ^{18}F on a phenyl ring, does not reasonably provide enablement for preparing all isotopically labeled compounds or compounds labeled with ^{18}F other than on a phenyl ring. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in

scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Synthesis of any particular labeled compound would require development of a separate synthetic route for each compound and for each different isotope. Considering the large number is possible isotopes, the specialized nature of the experiments depending upon if the isotope is radioactive or stable, if the isotope is an alpha emitter, a beta emitter, or a positron emitter, the differing half-lives involved and the large number of compounds of formula (I), a large degree of experimentation. Laboratory facilities suitable for synthesis of ^{13}C labels would not be suitable for ^{3}H. Laboratories suitable for ^{14}C labeling experiments would not be suitable for ^{18}F labeling, which requires immediate access to a cyclotron. b) The direction concerning the isotope synthesis is found in the passage spanning line 26, page 40 to line 10, page 41. This passage teaches only the synthesis of compounds with ^{18}F on a phenyl ring. No other isotopes are discussed. c) There are no working examples of a compound of formula (I) labeled

with any isotope. d) The nature of the invention is chemical synthesis, which involves chemical reactions. e) The state of the art is summarized by Sabbatini (The Cyclotron and PET), who teaches that ^{18}F has a half life of 110 minutes and that cyclotron is an essential piece of equipment for synthesis of ^{18}F labeled raduiopharmaceuticals. Thus, ^{18}F labeling is even more complex that normal radiopharaceutical synthesis. f) The artisan using Applicants invention would be a process chemist or radio-chemist with a BS degree in chemistry and several years of experience with the unusual ^{18}F nuclei. g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. h) The breadth of the claims includes all of the thousands of compounds of formulas I as well as the large number of different known isotopes.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

10. Claims 32-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating sleep/wake disorders, arousal/vigilance disorders, migraine, epilepsy, and narcolepsy, does not reasonably provide enablement for treating inhibiting H_3 receptor activity generally or treating other histamine receptor related disorders. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above. a) Determining if any particular claimed compound would treat any particular histamine related disorder disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning treating diseases is found in the lines 19-26 on page 6, the passage spanning line 16, page 16 to line 10, page 17, and lines 21-28, page 34 which merely states Applicants' intention to do so. More detailed intend for specific diseases is found in lines 1-30, page 36 but it is unclear if the references discussed establish any nexus between Applicants' single *in vitro* assay and clinical efficacy for any human disease treatment. Applicants describe

formulations in the passage spanning line 31, page 36 to line 11 page 37. Doses required to practice their invention are described in the passage spanning line 25, page 39 to line 9, page 40. A 2,000-fold range of doses is recommended. Since Applicants' assay is not capable of distinguishing agonists from antagonists, how is the skilled physician to know what dose to use for each of these different diseases? There is an *in vitro* assay described in the passage spanning line 13, page 81 to the end of page 84. As discussed in Phillips (Ann. Reports. Med. Chem.). H_3 agonists are used for different diseases than H_3 antagonists. Use of an H_3 antagonist for migraine treatment say would only worsen the condition. Thus, before any compound can be used therapeutically, its behavior at the receptor site must be understood to a finer level of understanding than provided by Applicants. There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in H_3 receptor diseases is provided by Phillips (Ann. Reports. Med. Chem.) who reports in the paragraph spanning pages 36-37, the second and fourth paragraphs on page 37, and the final paragraph on page 38 demonstrate that the allowed uses are art-recognized for H_3 receptor agonists and antagonists. The discussions of ischemia, cognition, ADHD, and eating disorders treatment discussed in other parts of this reference appears to

be speculative. Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual", or not provided in the specification, *Ex parte Jovanovics,* 211 USPQ 907, *In re Langer,* 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1 as well as the hundred of diseases embraced by the term histamine receptor disorder. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue

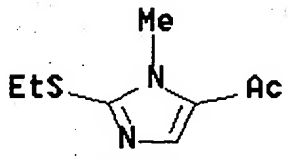
experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

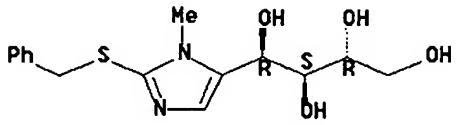
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7, 11, and 13-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Jordaan (Journal of Heterocyclic Chemistry). The compound shown below fits formula (I) with M = $C(=O)R^M$, R^M = methyl, Q^1 = methyl, A^3 = sulfur, L^3 = CH_2, and Q^3 = methyl. It has Registry Number 20970-45-0 and is found in lines 32-44, column 1, page 724 of the reference. It also fits formula (I) with L^3 = absent and Q^3 = ethyl. Thus, claim 16 is anticipated.

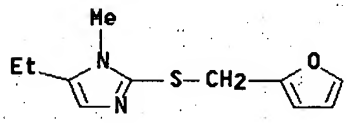


12. Claims 1-6, 11, and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Garcia Gonzalez (J., Carbohydrate Research). The compound shown below fits formula (I) with M = $CHOHR^M$, R^M = propyl substituted by

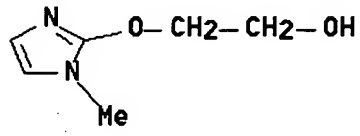
hydroxyl, Q^1 = methyl, A^3 = sulfur, L^3 = CH_2, and Q^3 = phenyl. It has Registry Number 35923-23-0 and is found in the scheme on page 437 of the reference. It is compound 10. Synthesis is taught in the third and fourth paragraph on page 439.



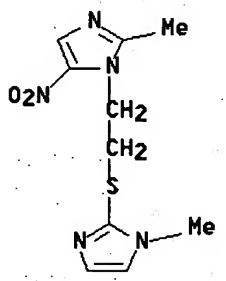
13. Claims 1-5, 11, and 13-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Tweit ('179). The compound shown below fits formula (I) with M = CH_2R^M, R^M = methyl, Q^1 = methyl, A^3 = sulfur, L^3 = CH_2, and Q^3 = 2-furanyl. It has Registry Number 40517-32-6 and is found in lines column 7 of the reference.



14. Claims 1, 3, 4, 11, 12, and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Kato (JP 02306237 A2). The compound shown below fits formula (I) with M = hydrogen, Q^1 = methyl, A^3 = oxygen, L^3 = CH_2, and Q^3 = methyl substituted by hydroxyl. It has Registry Number 138250-03-0 and is found in page 306 of the reference. It is compound 24 at the bottom of column 1 on that page. It also fits formula (I) with L^3 = absent and Q^3 = ethyl substituted by hydroxyl. Thus, claim 16 is anticipated.

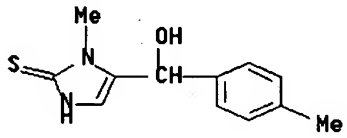


15. Claims 1, 3, 4, 13-15, 17, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Tweit ('160). The compound shown below fits formula (I) with M = hydrogen, Q^1 = methyl, A^3 = sulfur, L^3 = CH_2-CH_2, and Q^3 = 1-imidazolyl substituted by methyl and nitro. It has Registry Number 53064-88-3 and is found in lines 18-45, column 6 of the reference.



16. Claims 1, 3-6, 8-10, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Phillips (Synthesis). There are nine compounds in this reference, which teach Applicants' claims. The compound shown below fits formula (I) with M = $CHOHR^M$, R^M = phenyl substituted in the 4-position by methyl, Q^1 = methyl, A^3 = L^3 = absent, and Q^3 = sulfanyl. The word sulfanyl is derived from sulfane or H_2S. Thus, it means –SH. It has Registry Number 131470-52-5 and is found in the table on page 761 of the reference. It is compound 4a. The other anticipatory

compounds are 4b-4h and 4k. Synthesis of these compounds is found in the paragraph spanning pages 762-763 of the reference. The compound has been drawn by Chemical Abstracts in a tautomeric form with the tautomeric hydrogen atom on nitrogen rather than on sulfur. However, the authors of the reference draw it in its mercapto or sulfanyl form.



Allowable Subject Matter

17. The following is a statement of reasons for the indication of allowable subject matter: the compounds of claims 19-21 are patentable over Jones (2005/0250948 A1). Jones (2005/0250948 A1) teaches compounds of the formula (I) with $Q^3 = R^{31}R^{32}N$- but the date of this publication makes it an incompetent reference against Applicants' claims. Claims 40-45 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action.

Conclusion

18. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas McKenzie, Ph.D. whose telephone number is (571) 272-0670. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 9:00 to 5:30, Monday through Friday.

If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, James O. Wilson at (571) 272-0661. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas C. McKenzie, Ph.D.
Primary Examiner
Art Unit 1624

TCMcK
March 9, 2006